Patent Office
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I, LEANNE MYNOTT, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003904717 for a patent by DBL AUSTRALIA PTY LTD as filed on 01 September 2003.

WITNESS my hand this
Tenth day of September 2004

LEANNE MYNOTT
TEAM LEADER EXAMINATION
SUPPORT AND SALES

P/00/009
Regulation 3.2

AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: ORAL DRUG DELIVERY SYSTEMS

Applicant: DBL AUSTRALIA PTY LTD

The invention is described in the following statement:

ORAL DRUG DELIVERY SYSTEMS

Field of the Invention

The present invention relates to drug delivery systems that are suitable for oral delivery of one or more biologically active agents to an individual and which are capable of modifying bioavailability and/or release of the active agent. The present invention also relates to dosage forms incorporating the drug delivery system for oral administration and to methods for modifying the bioavailability and/or release of orally administered biologically active agents.

Background of the Invention

The goal of drug delivery systems is to provide an effective therapeutic amount of a biologically active agent ('active agent') to obtain and maintain a desired concentration of active agent. Classical drug delivery systems typically provide for rapid release of an active agent, which leads to the presence of maximal concentrations of the active agent in the blood followed by a rapid decrease in concentration as the active agent is metabolised and cleared. At these maximal concentrations, many active agents are highly toxic. Furthermore, if the concentration of active agent decreases rapidly in the body, then the time during which there is a therapeutically-effective level is short, and therapeutic efficacy requires administration of multiple doses which can lead to a reduced patient compliance.

Modified release drug delivery systems are designed to alter the temporal delivery of an active agent. Modified release drug delivery systems are those that provide an *in vivo* release profile (a 'modified release') of an active agent that is different from the *in vivo* release profile of the active agent without the modification (an 'immediate release'). The modified release may be a delayed, extended, pulsed or sustained release. By modifying the release of an active agent it may be possible to minimise side effects of the active agent or

decrease the frequency of dosing to improve patient compliance. For example, sustained release drug delivery systems provide a slow release of an active agent over an extended period of time. Traditionally, drug delivery systems (whether modified release or not) are administered either by the oral or parenteral routes. Administration by injection (parenteral administration) is favoured in many cases where active agents are unable to be effectively administered via the oral route due to relatively hostile environment in the gastrointestinal tract. However, in most cases oral administration is the most favourable route because it is the most convenient form of administration for patients. Therefore it will usually be preferred to administer an active agent orally in the form of a tablet or capsule, and most preferably in a way such that administration is once a day at the most. The present invention aims to provide drug delivery systems containing an active agent that are safe and efficacious when delivered orally and which modify absorption of the active agent *in vivo* after administration, and most preferably sustain the release of the active agent *in vivo* after administration.

Throughout this specification reference may be made to documents for the purpose of describing the background to the invention or for describing aspects of the invention. However, no admission is made that any reference, including any patent or patent document, cited in this specification constitutes prior art. In particular, it will be understood that, unless otherwise stated, reference to any document herein does not constitute an admission that any of these documents form part of the common general knowledge in the art in Australia or in any other country. The discussion of the references states what their authors assert, and the applicant reserves the right to challenge the accuracy and pertinency of any of the documents cited herein.

Summary of the Invention

The present invention provides a method of modifying the absorption of a biologically active agent in the gastrointestinal tract of an animal, the method including the step of administering to the gastrointestinal tract of the animal:

(i) a composition including a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase formed from a surfactant and containing the biologically active agent,

wherein the surfactant is not glyceryl monooleate or glyceryl monolinoleate.

Preferably, the lyotropic phase is a reverse lyotropic phase.

The methods of the present invention may provide one or more of the following effects: controlled release of the active agent in the gastrointestinal tract, protection of the active agent from enzymatic or chemical degradation in the gastrointestinal tract, protection of the active agent from dissolution or slowing of the dissolution process in the gastrointestinal tract, localisation and maintenance of locality of the active agent in the gastrointestinal tract, enhanced bioavailability, enhanced solubility in the gastrointestinal tract, a less toxic alternative to known formulations, benefits in processing, handling and/or administration compared to current therapies. For the purpose of this document, toxic is meant in its general sense, but includes adverse reaction to the excipients, drugs, or materials, such as cardiotoxicity, immunological response, allergic response, genotoxicity, carcinogenicity, nephrotoxicity, anaphylaxis, and cytotoxicity. Cardiotoxicity is of particular interest, as many biological agents delivered orally cause cardiotoxicity due to high peak plasma levels, for which a modified release system would be particularly beneficial in preventing.

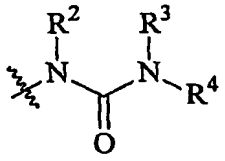
For compounds which are susceptible to undesirable chemical or biochemical reactions, such as hydrolysis, degradation or inactivation, the present invention may provide a protective environment for the active agent, thereby permitting therapeutic levels of active agent in plasma to be achieved.

The present invention also provides a method of modifying the absorption of a biologically active agent in the gastrointestinal tract of an animal, the method including the step of administering to the gastrointestinal tract of the animal:

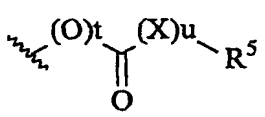
(i) a composition including a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with aqueous solutions; or

(ii) a lyotropic phase containing the biologically active agent,

wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



(I)



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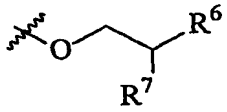

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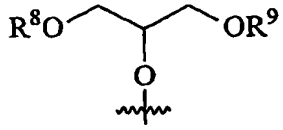

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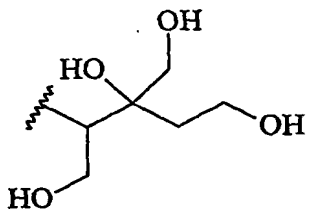

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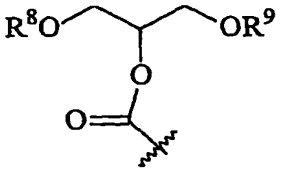

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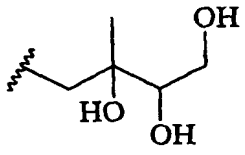


(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,
R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,
t and u are independently 0 or 1,
R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,
R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

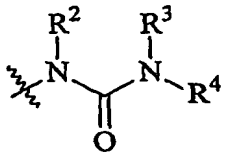
in structure (IV) and (VI) R^8 is –H or –alkyl,
R^9 is –H or –alkyl.

The present invention also provides a method of modifying the release of a biologically active agent in the gastrointestinal tract of an animal, the method including the step of administering to the gastrointestinal tract of the animal:

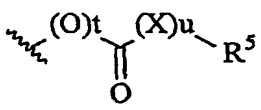
(i) a composition including a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase containing the biologically active agent,

wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



(I)



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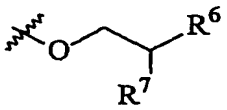

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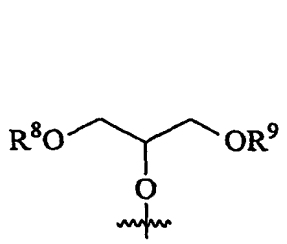

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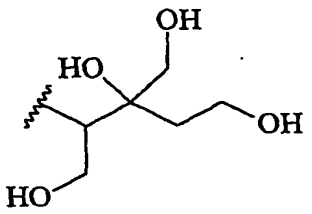

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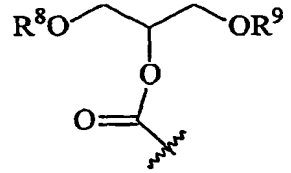

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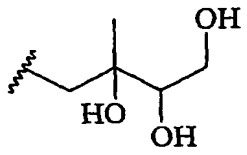


(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,

R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,

t and u are independently 0 or 1,

R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,

R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

in structure (IV) and (VI) R^8 is –H or –alkyl,

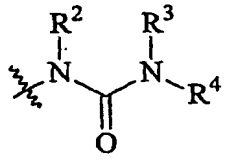
R^9 is –H or –alkyl.

The present invention also provides a method for sustaining the release of a biologically active agent in the gastrointestinal tract of an animal, the method including the step of administering to the gastrointestinal tract of the animal:

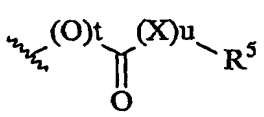
(i) a composition including a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase containing the biologically active agent,

wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



(I)



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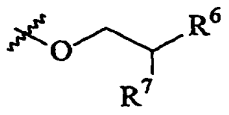

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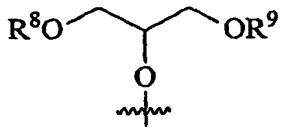

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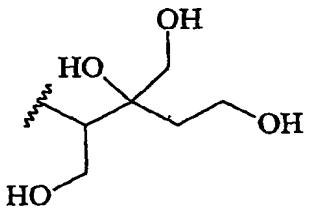

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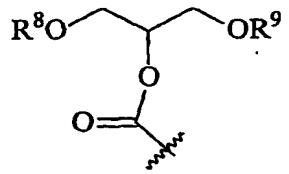

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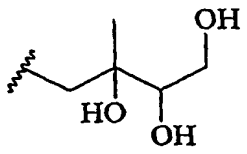


(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,
R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,
t and u are independently 0 or 1,
R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,
R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

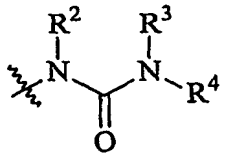
in structure (IV) and (VI) R^8 is –H or –alkyl,
R^9 is –H or –alkyl.

The present invention also provides a method of protection of a biologically active agent from detrimental effects of the gastrointestinal environment of an animal, the method including the step of administering to the gastrointestinal tract of the animal:

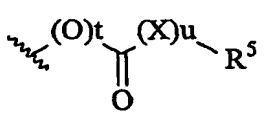
(i) a composition including a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase containing the biologically active agent,

wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



(I)



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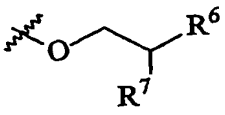

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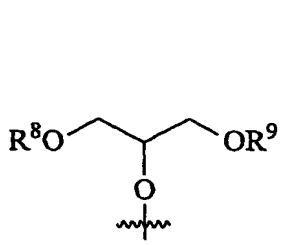

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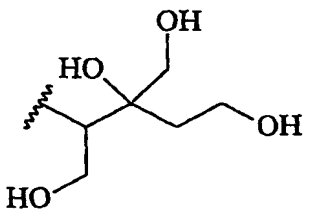

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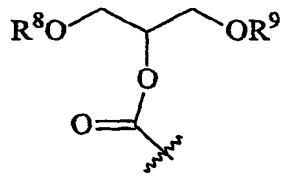

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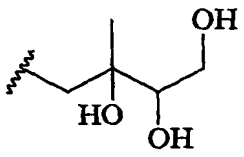


(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,

R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,

t and u are independently 0 or 1,

R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,

R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

in structure (IV) and (VI) R^8 is –H or –alkyl,

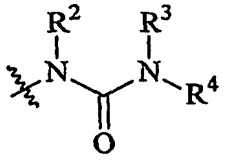
R^9 is –H or –alkyl.

The present invention further provides a composition suitable for oral delivery of a biologically active agent to an animal, the composition including:

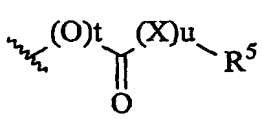
(i) a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase containing the biologically active agent,

wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



(I)



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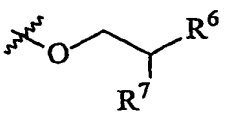

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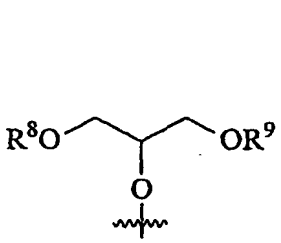

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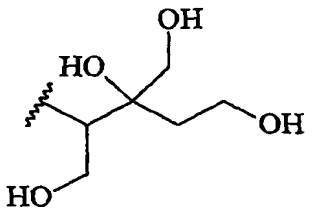

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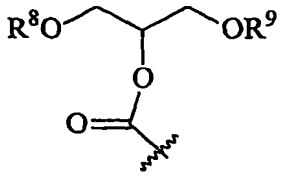

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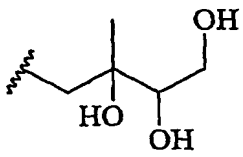


(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,

R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,

t and u are independently 0 or 1,

R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,

R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

in structure (IV) and (VI) R^8 is –H or –alkyl,

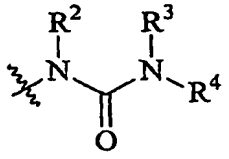
R^9 is –H or –alkyl.

The present invention also provides an oral drug delivery system for modifying the absorption of a biologically active agent in the gut of an animal, the drug delivery system including:

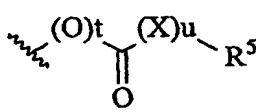
(i) a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase containing the biologically active agent,

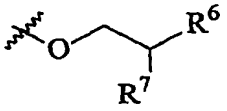
wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



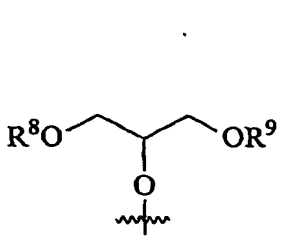
(I)



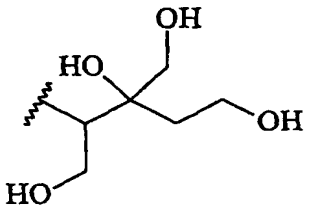
(II)



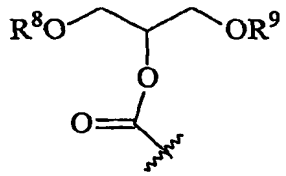
(III)



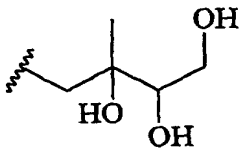
(IV)



(V)



(VI)



(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,

R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,

t and u are independently 0 or 1,

R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,

R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

in structure (IV) and (VI) R^8 is –H or –alkyl,

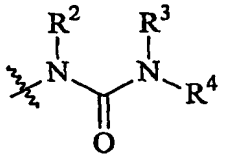
R^9 is –H or –alkyl.

The present invention also provides an oral drug delivery system for modifying the release of a biologically active agent in the gut of an animal, the drug delivery system including:

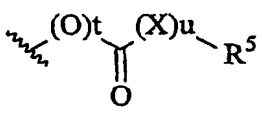
(i) a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase containing the biologically active agent,

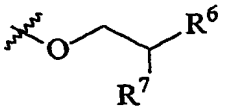
wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



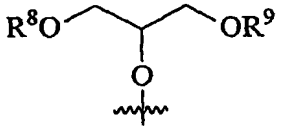
(I)



(II)



(III)



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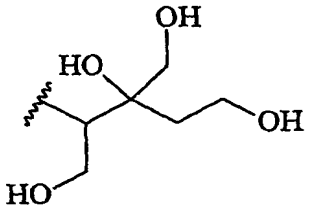
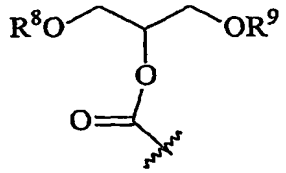
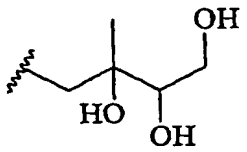


(V)



(VI)



(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,
R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,
t and u are independently 0 or 1,
R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,
R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

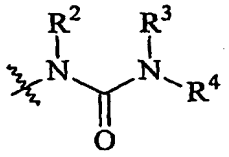
in structure (IV) and (VI) R^8 is –H or –alkyl,
R^9 is –H or –alkyl.

The present invention also provides an oral drug delivery system for sustaining the release of a biologically active agent in the gut of an animal, the drug delivery system including:

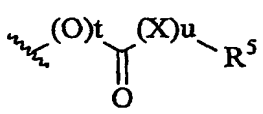
(i) a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase containing the biologically active agent,

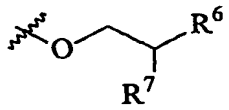
wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



(I)



(II)



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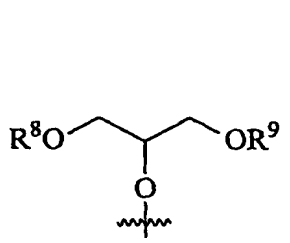
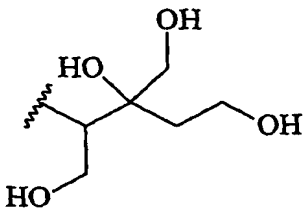
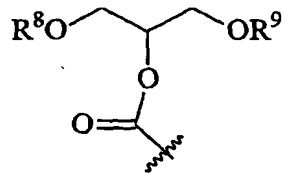


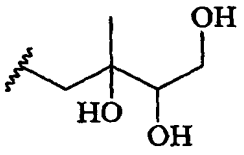
(IV)



(V)



(VI)



(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,

R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,

t and u are independently 0 or 1,

R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,

R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

in structure (IV) and (VI) R^8 is –H or –alkyl,

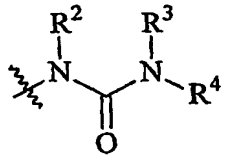
R^9 is –H or –alkyl.

The present invention also provides a drug delivery system for the oral delivery of a biologically active agent in the gut of an animal, the drug delivery system including:

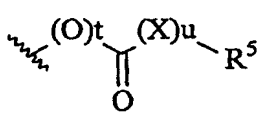
(i) a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase containing the biologically active agent,

wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



(I)



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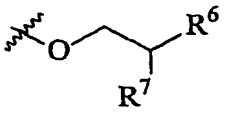
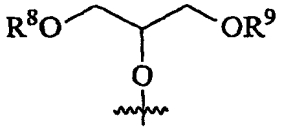


(III)



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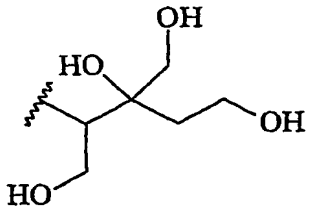

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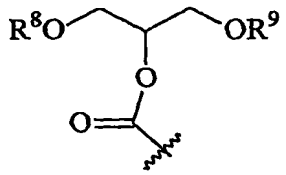
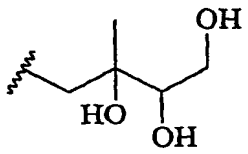


(VI)



(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,
R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,
t and u are independently 0 or 1,
R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,
R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

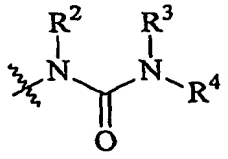
in structure (IV) and (VI) R^8 is –H or –alkyl,
R^9 is –H or –alkyl.

The present invention also provides an oral drug delivery system for the protection of a biologically active agent from the detrimental effects of the gastrointestinal environment of an animal, the drug delivery system including:

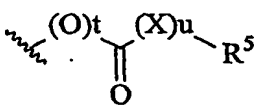
(i) a composition including a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids; or

(ii) a lyotropic phase containing the biologically active agent,

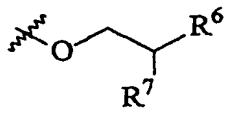
wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



(I)



(II)



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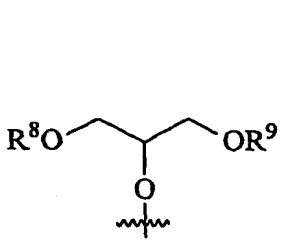
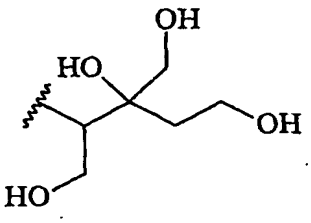
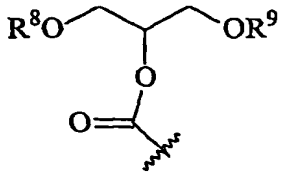


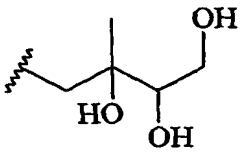
(IV)



(V)



(VI)



(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$ or another tail group as defined herein,

R^3 and R^4 are independently selected from one or more of –H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$

in structure (II) X is O, S or N,

t and u are independently 0 or 1,

R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$, $-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl), $-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$, $-CH_2(CHOH)_2CH_2OH$, or $-CH_2C(O)NHC(O)NH_2$,

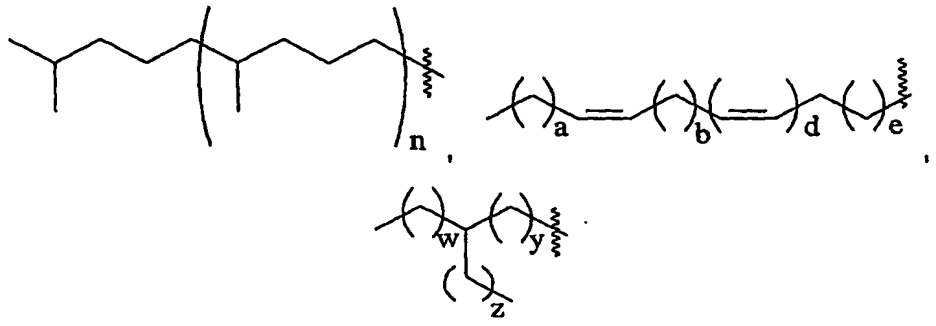
in structure (III) R^6 is –H or –OH,

R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$, and

in structure (IV) and (VI) R^8 is –H or –alkyl,

R^9 is –H or –alkyl.

In the surfactants described herein the tail is preferably selected from:



wherein n is an integer from 2 to 6, a is an integer from 1 to 12, b is an integer from 0 to 10, d is an integer from 0 to 3, e is an integer from 1 to 12, w is an integer from 2 to 10, y is an integer from 1 to 10 and z is an integer from 2 to 10.Preferred surfactant tails are hexahydrofarnesane ((3,7,11-trimethyl)dodecane), phytane ((3,7,11,15-tetramethyl)hexadecane), oleyl (octadec-9-enyl) or linoleyl (octadec-9,12-dienyl) chains.

According to the present invention, the composition may be incorporated into a dosage form. The dosage form may also contain other additives or excipients that are known to those skilled in the relevant art.

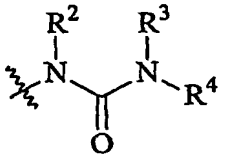
The present invention also provides an oral delivery system that provides for multiphase release of the active agent. For example, compositions containing the lyotropic phase or a surfactant which forms a lyotropic phase on contact with polar liquids may contain a domain that is extraneous to the lyotropic phase. The extraneous domain may contain the active agent and the kinetics of the release of active agent from the extraneous domain may be different to the release of the active from the lyotropic phase. The active agent may be contained in or may form the extraneous domain. In the extraneous domain all or some of the active agent may be in the form of a solid crystalline particle, an

amorphous particle, and/or a solution in a solid or liquid that is immiscible with the surfactants described herein. Alternatively, or in addition the active agent may be encapsulated in a polymeric particle.

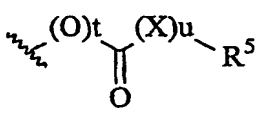
General Description of the Invention

The surfactants that are used in compositions of the present invention are amphiphilic compounds in which the head group forms a charged or uncharged hydrophilic polar region and the tail forms a hydrophobic non-polar region.

The surfactants of the present invention preferably contain a head group selected from the group consisting of any one of structures (I) to (VII):



(I)



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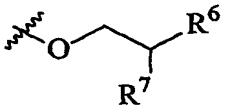

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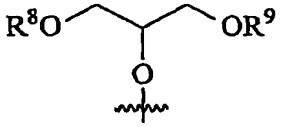

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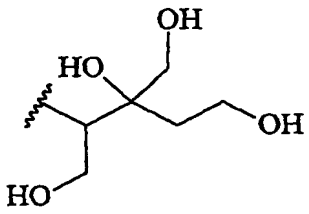

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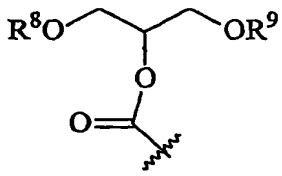

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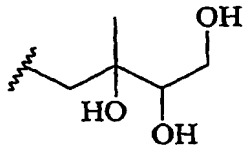


(VII)

and preferably contain a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is –H, $-CH_2CH_2OH$, or another tail group,
R^3 and R^4 are independently selected from one or more of
–H, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$,

in structure (II) X is O, S or N,
t and u are independently 0 or 1,
R^5 is $-C(CH_2OH)_2$alkyl, $-CH(OH)CH_2OH$,
$-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl),
$-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$,
$-CH_2(CHOH)_2CH_2OH$, or
$-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is –H or –OH,
R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$,

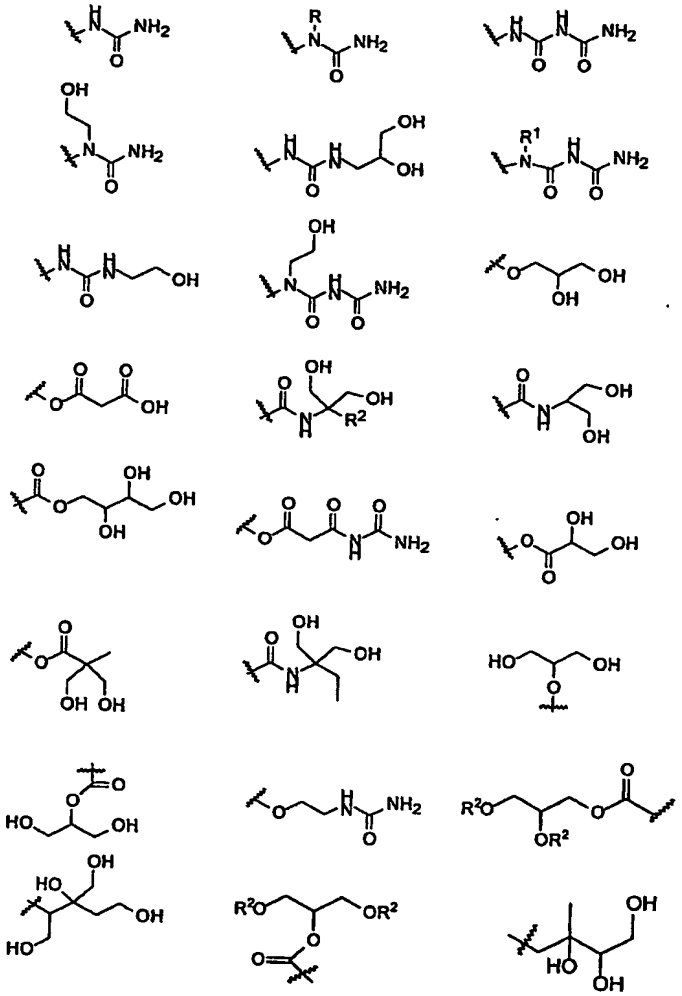
in structures (IV) & (VI) R^8 is –H or –alkyl,
R^9 is –H or –alkyl.

Preferred surfactant tails are hexahydrofarnesane ((3,7,11-trimethyl)dodecane), phytane ((3,7,11,15-tetramethyl)hexadecane), oleyl (octadec-9-enyl) or linoleyl (octadec-9,12-dienyl) chains.

Preferred surfactant head groups are shown in Table 1.

Combinations of the preferred tails and head groups have either been synthesised and demonstrated to specifically form or are expected to form stable lyotropic phases in excess water based on data obtained from the surfactants that have been synthesised to date.

Table 1



In an aqueous surfactant mixture, water is associated with the head groups of the surfactant which leads to the formation of fluid hydrophilic domains in the mixture. The hydrophobic tails of the surfactant are also screened from the water by the hydrophilic head groups to thereby form a hydrophobic domain. The fluidity of the hydrophilic domain allows the native geometry of the surfactant molecule to determine the orientation, and spatial aspects of arrangement of the surfactant molecules at the interface between the hydrophilic and hydrophobic domains. This arrangement is often called the 'curvature', because the interface can be curved towards the hydrophilic or hydrophobic domains. The hydrophilic and hydrophobic domains are

sometimes referred to as the water and oil domains, respectively. The addition of greater amounts of water to the surfactant alters the average curvature of the interface, potentially resulting in a variety of particular topologies that can be displayed by a surfactant-aqueous system at equilibrium. At equilibrium, these topologies are often termed 'mesophases', 'lyotropic phases', 'liquid crystalline phases', or just 'phases'. Examples of the particular topologies that can be formed in surfactant-aqueous systems include micellar (normal or reverse), hexagonal (normal or reverse), lamellar, and cubic (normal, reverse or bicontinuous), among others.

Micellar phase includes micelles which form when surfactant molecules self-assemble to form aggregates due to the head groups associating with water, and the tails associating with other tails to form a hydrophobic environment.

Normal and reverse micelles may be spherical, rod-like or disk shaped, depending on the molecular geometry of the surfactant, but at low enough concentration the system is essentially isotropic. In the case of reverse micelles, the addition of water to the system will result in either phase separation of a separate water phase, due to a limited capacity to incorporate the excess water, or conversion to a different phase, such as reverse hexagonal phase. In the spectrum of possible topologies formed as described above, reverse micellar phase is generally regarded as a low viscosity phase.

Reverse hexagonal phase is the oil continuous version of the normal hexagonal phase, with water-core micelles in a close packed hexagonal array, and is generally regarded as a high viscosity phase.

Cubic phase consists of two main types, bicontinuous and micellar. Normal and reverse cubic phases of the micellar type consist of close packed spherical micelles in a cubic array, where either the water and headgroups, or the tails form the interior of the micelles. They are generally of high viscosity, but because they consist of spherical micelles these systems are isotropic, so no birefringent texture is observed.

Bicontinuous cubic phases form when the molecular geometry of a surfactant molecule is well balanced, such that the net curvature is zero. This results in a so-called 'infinite periodic lattice structure', in which the hydrophobic and hydrophilic domains are intertwined but do not intersect. The bicontinuous cubic phases, while consisting of bilayers, have long range order based on a cubic unit cell, and hence are also seen to be isotropic when viewed through crossed polarised light. Reverse bicontinuous cubic phases are generally regarded as high viscosity phases. For the purposes of the present invention, bicontinuous phases may be considered 'lyotropic phases', 'reverse lyotropic phases' or 'reverse liquid crystalline phases'.

Preferably, the oral drug delivery system of the present invention contains a surfactant capable of forming a lyotropic phase that is selected from the group consisting of a reverse micellar phase, a bicontinuous cubic phase, a reverse intermediate phase and a reverse hexagonal phase, or contains a lyotropic phase that is selected from the group consisting of a reverse micellar phase, a bicontinuous cubic phase, a reverse intermediate phase and a reverse hexagonal phase. Most preferably the reverse lyotropic phase that is formed is a reverse micellar phase, a reversed hexagonal phase or a bicontinuous cubic phase.

As described previously, the present invention provides a method of modifying the release of a biologically active agent in the gastrointestinal tract of an animal. The method includes the step of administering to the gastrointestinal tract of the animal a composition including a surfactant capable of forming a lyotropic phase containing the biologically active agent on contact with polar liquids, or a lyotropic phase containing the biologically active agent wherein the lyotropic phase is formed from a surfactant which is poorly digested in the gastrointestinal tract. This provides a composition which is poorly digested within the gastrointestinal tract, providing a persistent, protective reservoir from which active agent may be released and may result in differing absorption from

active agent administered in other ways. Whilst surfactants having structures described herein in detail may be poorly digested in the gastrointestinal tract, it is possible that surfactants other than glyceryl monooleate that do not fall within the ambit of the structural formulae provided may also exhibit poor digestability and an ability to form lyotropic phases, thus making them suitable for use in the methods of the present invention.

It has previously been shown that lyotropic phases of the type formed by the surfactants described herein may exhibit mucoadhesive properties. In addition, *in vitro* studies have shown that some of the surfactants described herein are poorly digested compared to typical formulation lipids. As a result, by using the methods of the present invention it is possible to form a sustained release drug delivery system that provides a persistent solubilising reservoir under digestion conditions from which the absorption of active agents can occur.

As used herein the term 'modified absorption' means that absorption of the active agent from the composition is different to that of the active agent alone or in solution, or in another dosage form. It will be appreciated that in the compositions of the present invention the active agent is not necessarily covalently bound to the surfactant. Rather, the active agent may be dissolved, complexed or in a complex form, or in a salt form, and is included within the lyotropic phase and it may reside in the hydrophobic domain, the hydrophilic domain, or in the interfacial region of the lyotropic phase. Alternatively, the active agent may be distributed between the various domains by design or as a result of the natural partitioning processes. If the active agent is amphiphilic it may reside in one or any number of these domains simultaneously. Alternatively the active agent be dissolved in the surfactant itself, which may or may not contain other additives, such as solubility enhancers and stabilisers.

As used herein the term 'modified release' means that release of the active agent from the composition is either delayed or sustained and the timing of

release of the active agent is different to that of the active agent alone or in solution, or in another dosage form.

As used herein the term 'improved bioavailability' means that the mass of active agent reaching the systemic circulation, when administered in the form of the invention, is greater than that of the active agent alone or in solution, or in another dosage form.

As used herein the term 'protection of the active agent ' means that the active agent is physically or chemically protected from undesirable reactions which may occur in any part of the gastrointestinal tract, to which the active agent may otherwise be susceptible when administered alone or in solution, or in another dosage form. It will be recognised that administration in another dosage form may provide greater protection from such effects than the invention, but may not provide other benefits of the invention described herein.

As used herein the term 'localisation of the active agent ' means that the active agent is physically or chemically localised to specific areas of the gastrointestinal tract for a time longer than would be expected if administered alone, in solution or in another dosage form. This may or may not be the result of mucoadhesion. It will be recognised that administration in another dosage form may provide better or longer localisation than the invention, but may not provide other benefits of the invention described herein.

As used herein the term 'polar liquid' means polar solvents including but not limited to water, glycerol, propylene glycol, propylene carbonate, methanol, ethanol, glycofurol and the like, and solutions based on these liquids, and mixtures thereof.

The thermodynamic stability of the lyotropic phases to dilution in excess aqueous solution means that they can be dispersed to form particles of the lyotropic phase. Particles containing cubic phase or hexagonal phase are

sometimes referred to as cubosomes or hexosomes, respectively. For many applications it is advantageous for the compositions to be a colloidal solution or suspension of the lyotropic phase containing the biologically active agent, suspended in a suitable liquid carrier. Most preferably the liquid carrier is water. Alternatively the composition may be a freeze-dried, spray freeze-dried, lyophilised or spray-dried powder comprised in part of particles loaded with active agent. The dried powder may be compressed into a tablet dose form or filled into a capsule to facilitate convenient administration.

The 'active agent' or 'biologically active agent' that is used in compositions of the present invention may be any substance that is intended for use in the diagnosis, cure, mitigation, treatment or prevention of an undesirable state in an individual animal. For example, the active agent may be a drug that is used therapeutically to treat or prevent a disease state in humans or other animal species.

The composition of the present invention may be particularly suitable for the delivery of insoluble or poorly soluble active agents, and in particular poorly soluble pharmaceutically active agents for human and veterinary medicine.

Examples of some poorly soluble pharmaceutically active agents that could be included in compositions of the present invention include immunosuppressive agents such as cyclosporins including cyclosporine (cyclosporin A), immunoactive agents, antiviral and antifungal agents, antineoplastic agents, analgesic and anti-inflammatory agents, antibiotics, anti-epileptics, anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, anticonvulsant agents, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergic and antiarrhythmics, antihypertensive agents, hormones, and nutrients. A detailed description of these and other suitable agents may be found in Remington's Pharmaceutical Sciences, 18th edition, 1990, Mack Publishing Co. Philadelphia, Pa.

Importantly, the present invention allows for the incorporation of agents of very different physico-chemical properties into a single dosage form. Because the invention comprises hydrophilic, hydrophobic, and interfacial domains, the incorporation of hydrophilic, lipophilic, hydrophobic and amphiphilic compounds in any combination is possible, and the release of all of these materials may be controlled. This provides the invention a particular advantage over other forms of delivery systems, such as emulsions, liposomes, and polymeric encapsulation systems.

In the case of hydrophilic biologically active agents, which will preferentially reside in the aqueous domains of the lyotropic phase formed by the surfactants described earlier, the environment may provide protection of hydrophilic agents from the detrimental effects of the external gastrointestinal environment. This may inhibit or prevent undesirable chemical or biochemical reactions which may otherwise degrade, destroy or inactivate the agent when not administered in a composition of the invention. This protection allows more agent to be absorbed in its active form, and consequently provides for increased bioavailability. Examples of such hydrophilic active agents would include but not be limited to peptides and proteins, and other agents such as vaccines.

The composition of the present invention may be particularly suitable for the controlled release delivery of agents that cannot otherwise be effectively administered by the oral route to human patients because of poor or inconsistent systemic absorption from the gastrointestinal tract, or poor stability in the gastrointestinal environment. These agents are currently administered via intravenous routes, requiring intervention by a physician or other health care professional, entailing considerable discomfort and potential local trauma to the patient and even requiring administration in a hospital setting.

An example of an active agent that currently requires administration by intravenous infusion is paclitaxel. Paclitaxel is currently marketed as TAXOL™

and it is one of the important classes of cytotoxic agents which are not normally bioavailable when administered orally to humans. In addition to poor oral bioavailability, the toxicity of paclitaxel means that it has to be administered over an extended period of time in order to reduce the toxic effects of the dosage. Accordingly, paclitaxel (and many other chemotherapeutic drugs) is typically administered by continuous intravenous infusion, which may take several hours. Compositions of the present invention provide alternative administration regimes, in which release of an active agent from the invention, administered orally can be sustained *in vivo.* As a consequence of the sustained release the active agent may not have to be administered as frequently.

The delivery of agents that cannot be effectively administered by the oral route to human patients because of poor or inconsistent systemic absorption from the gastrointestinal tract, or poor stability in the gastrointestinal environment, may also be accomplished by incorporation of the active agent into an oral dosage form of the present invention. Controlled release of the active agent may be of additional therapeutic benefit for some active agents given by this route, particularly those with short half-lives *in vivo*, or those for which high doses may be toxic. Potential oral dosage forms could include a capsule containing the bulk form of the present invention, a capsule containing a dispersion of the present invention, a capsule containing a powdered form of the invention, or a capsule containing a precursor solution of the present invention that forms the invention on ingestion. The capsules may or may not contain other materials and may or may not be enterically coated. An alternative to the capsule form is a non-encapsulated syrup or other liquid form of the invention that is administered by drinking or via intragastrically or intraenterically intubating the patient.

Formulations for oral ingestion are in the form of tablets, capsules, pills, ampoules of powdered active agent, or oily or aqueous suspensions or solutions. Tablets or other non-liquid oral compositions may contain acceptable excipients, known to the art for the manufacture of pharmaceutical

compositions, comprising diluents, such as lactose or calcium carbonate; binding agents such as gelatin or starch; and one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring or preserving agents to provide a palatable preparation. Moreover, such oral preparations may be coated by known techniques to further delay disintegration and absorption in the gastrointestinal tract.

Suspensions in polar liquids may contain the active ingredient in admixture with pharmacologically acceptable excipients, comprising suspending agents, such as methyl cellulose; and wetting agents, such as lecithin or long-chain fatty alcohols. The suspensions in polar liquids may also contain preservatives, colouring agents, flavouring agents and sweetening agents in accordance with industry standards.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, or dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol, sorbic acid, EDTA and the like. Cryoprotectants, spray drying adjuvants, such as starches and dextrans, buffers, and pH adjusting materials may also be contained in the compositions of the invention.

The compositions may also be subjected to further treatment processes to render them suitable for use in a particular application. For example, compositions may be processed by various means, such as homogenisation, sonication and extrusion, so as to achieve a satisfactory particle size distribution and surface properties.

Colloidal particles or compositions containing them may be further stabilised using a stabilising agent. A variety of agents suitable for this purpose are commonly used in other colloidal systems and may be suitable for the present purposes. For example, poloxamers, phospholipids, alginates, amylopectin and

dextran may be used to enhance stability. Addition of a stabilising agent preferably does not affect the final structure or the physical properties of the particles or compositions.

Compositions of the present invention may also be modified by the addition of additives, such as glycerol, sucrose, phosphate buffers, dextrose, sorbitol and saline in appropriate concentrations, to the aqueous medium without changing the principal structure of the particles.

It is contemplated that the attending clinician will determine, in his or her judgement, an appropriate dosage and regimen, based on the patient's age and condition as well as the severity of the condition that is being treated.

Description of the Figures

Aspects of preferred embodiments of the invention are shown in the accompanying figures. However, it is to be appreciated that the figures and the following description is not to limit the generality of the invention.

Figure 1 shows the plasma cinnarizine concentration over 30 hours following oral administration of approximately 10 mg of cinnarizine as an (i) aqueous suspension (○),(ii) cinnarizine dissolved in 2,3-dihydroxypropionic acid octadec-9-enyl ester (●), and (iii) cinnarizine dissolved in Myverol 18-99K (▼) in rats (n=3, average±s.e.).

Figure 2 shows the plasma cinnarizine concentration over 120 hours following oral administration of cinnarizine dissolved in 2,3-dihydroxypropionic acid octadec-9-enyl ester in rats (n=4, average±s.e) .

Description of Preferred Embodiments of the Invention

Example 1 - In Vivo Studies

Two in vivo studies in rats were conducted in which the oral absorption of a model lipophilic drug, cinnarizine was investigated.

Example 1.1

Study 1 involved the oral administration of three different dosage forms to three different treatments groups.

Treatment 1 was cinnarizine as an aqueous suspension containing solid cinnarizine, 0.4% Tween 80 and 0.5% hydroxypropyl methyl cellulose. Approximately, 10 mg of cinnarizine was administered to each rat (male, Sprague-Dawley, 250-300g) by oral gavage.

Treatment 2 was cinnarizine dissolved in 2,3-dihydroxypropionic acid octadec-9-enyl ester at 25 mg/g. Approximately, 400 mg of the lipid dose was administered to each rat (male, Sprague-Dawley, 250-300g) by oral gavage.

Treatment 3 was cinnarizine dissolved in Myverol 18-99K (a common well digested formulation lipid, which forms a viscous reverse cubic phase on contact with polar liquids) at 25 mg/g. Approximately, 400 mg of the lipid dose was administered to each rat (male, Sprague-Dawley, 250-300g) by oral gavage.

On the day prior to dosing, a cannula was surgically inserted into the left or right carotid artery to enable serial blood sampling. Rats were fasted prior to surgery and dosing, but water was freely accessible. Food was only allowed 8 hours after dosing. Blood samples were obtained via the indwelling cannula inserted

in the carotid artery for up to 30 hours post-dosing and plasma was separated by centrifugation. The plasma concentration of cinnarizine was determined by HPLC using a validated extraction procedure, with flunarizine as an internal standard and fluorescence detection.

Figure 1 illustrates the combined results from Study 1. Note the low residual drug concentration in the case of the suspension and Myverol 18-99K at 24 and 30 hours compared with in 2,3-dihydroxypropionic acid octadec-9-enyl ester which clearly shows elevated levels of drug.

Example 1.2

Study 2 was initiated after the data from Example 1.1 indicated that high cinnarizine levels in plasma were still apparent 30 hours post-dosing. Study 2 involved the same formulation/dosing regime of 2,3-dihydroxypropionic acid octadec-9-enyl ester as the first study however, plasma samples were obtained at more regular intervals between 8 hours and 24 hours, and were taken up to and including 120 hours. To be more certain of the results four rats instead of three were used for this study. On sacrifice, sections of the duodenum, jejunum and ileum were removed for histopathological examination for indications of gross changes to intestinal structure.

Figure 2 illustrates that a consistently high second peak is obtained in the plasma profile of all four rats studied. The initial peak is similar to that in Figure 1. This indicates that the invention may be useful for modifying the absorption of drug after oral administration compared to a suspension (representative of a tablet) or formulation in a representative formulation lipid (Myverol). The results also indicated that the invention may be useful for sustained release of a lipophilic drug, or for pulsatile release of a lipophilic drug.

The following pharmacokinetic data were obtained from these two studies. AUC values were derived using the linear trapezoid rule:

Vehicle	Dose (mg)	AUC_{0-t} (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hrs)	F (%vs susp)[1]
Data from 30 hour study, t=30					
2,3-dihydroxypropionic acid octadec-9-enyl ester	8.8±0.2	5063±752	250±21	30	190
Myverol	8.9±0.4	2957±640	230±30	2.5	110
Suspension	6.0±0.1	1819±614	277±64	2.0	100
Data from 72 hour study					
2,3-dihydroxypropionic acid octadec-9-enyl ester					
Data 0-72 hours					
Data 0-16 hours	9.6±0.3	**9742**±1059	230±47	**36**	**335**
Data 0-30 hours		*841±121*	*88±14*	*4.0*	
		2126±305			

[1] Relative bioavailability versus suspension set to 100%, calculated using:

$$F = \frac{AUC_{treatment}}{AUC_{suspension}} * \frac{Dose_{suspension}}{Dose_{treatment}}$$

The above table also illustrates that the invention may be useful for improving bioavailability of drug when administered in a composition of the invention compared to administration in another dose form.

Example 2 - Histopathology

In order to be useful for an oral delivery system, the invention must not cause undesirable pathological changes to the gastrointestinal tract after administration. This example illustrates the results of ranking of intestinal sections taken from 3 rats which received 2,3-dihydroxypropionic acid octadec-9-enyl ester described in Example 1.2, compared with 2 rats which did not receive 2,3-dihydroxypropionic acid octadec-9-enyl ester, but were otherwise maintained on the same diet and under the same conditions, and subjected to

the same surgical procedures as the treated rats for 120 hours after the time of dosing of the treatment group. The sections of intestine were immediately fixed in formalin buffer, blinded by coding, and graded by a veterinary pathologist by the criteria listed in the table following.

5

	Treatment group			No exposure	
	Rat A	Rat B	Rat C	Rat D	Rat E
Duodenum					
Mucus/debris	0	1	1	1	0
Villus shortening	0	1	2	1	1
Erosion	0	1	2	1	0
Epithelial swelling	1	0	2	0	0
Epithelial flattening	0	0	0	0	0
Goblet cell	0	0	0	0	0
Jejunum					
Mucus/debris	0	2	1	2	1
Villus shortening	1	1	0	2	2
Erosion	0	1	1	1	2
Epithelial swelling	0	1	1	1	1
Epithelial flattening	1	1	0	2	2
Goblet cell	1	0	1	2	2
Ileum					
Mucus/debris	1	3	1	0	3
Villus shortening	1	3	2	2	3
Erosion	0	3	1	1	3
Epithelial swelling	0	2	0	0	1
Epithelial flattening	0	0	1	2	3
Goblet cell	1	1	1	2	1

Rat intestinal tissue samples ranked 0-3 for each criteria in blinded fashion (0 = No effect, 3= severe effect), according to Swenson et. al, Pharm. Res. 11 (1994) 1132.

According to the examination of the rat intestinal tissue, no adverse effect on tissue pathology could be attributed to exposure to the invention, thereby demonstrating its potential use as a drug delivery system for oral administration.

Finally, there may be other variations and modifications made to the preparations and methods described herein that are also within the scope of the present invention.

DATED: 1 September 2003
PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
DBL AUSTRALIA PTY LTD

Figure 1

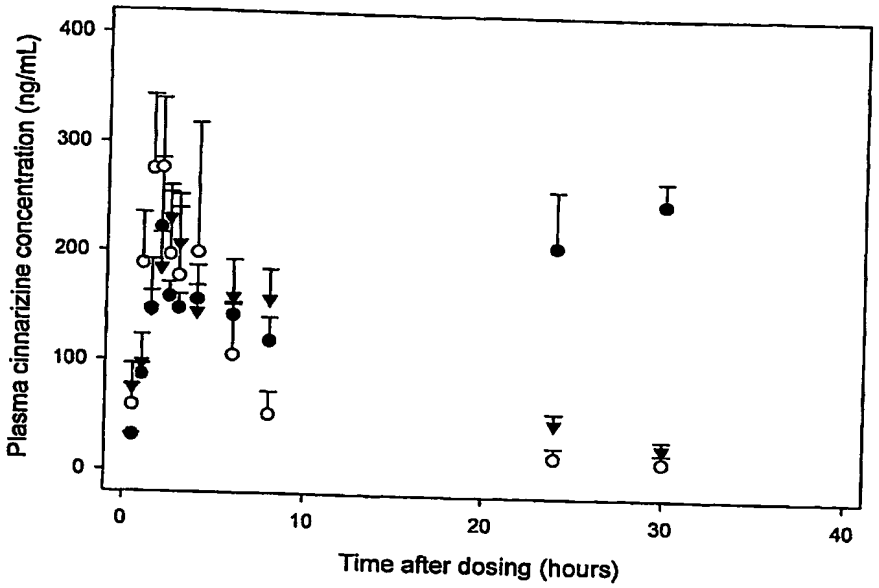
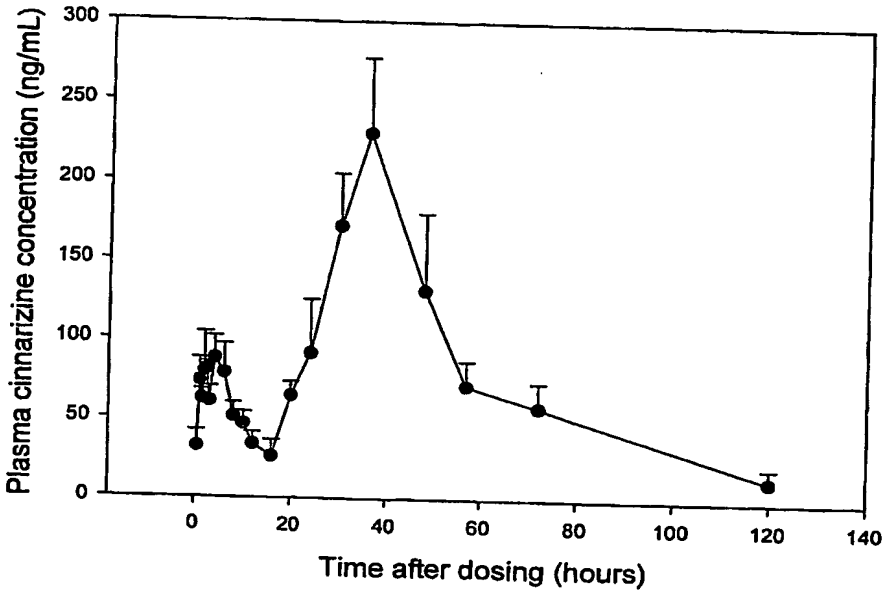


Figure 2



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